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Human Domain Antibody Therapeutics

Domantis is a drug discovery company developing the next generation of antibody molecules: Human Domain Antibodies.

Domain Antibodies (dAbs) are therapeutic molecules that have benefits of both small molecules and conventional antibodies. Like small molecules, dAbs are small in size and highly stable, resulting in a choice of therapeutic formats, delivery formulations and manufacture options. And like human antibodies, dAbs can be designed to have specificity and high affinity for the biological target of interest.

Domantis has more than a dozen proprietary Domain Antibody therapeutic programs, primarily in the fields of inflammation and oncology. These therapeutic leads include dAbs that uniquely neutralise (but not agonise) cytokine receptor targets, and Dual Targeting dAbs that can bind two therapeutic targets in one easily produced molecule. Domantis will take several Domain Antibody product leads into clinical testing on its own and will advance others through strategic alliances and co-development arrangements.

Due to its exclusive intellectual property and technology position for Domain Antibodies, Domantis is the only company capable of fully exploiting human Domain Antibodies.

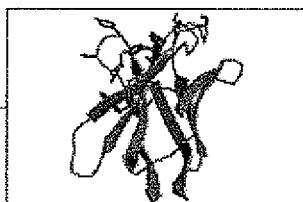


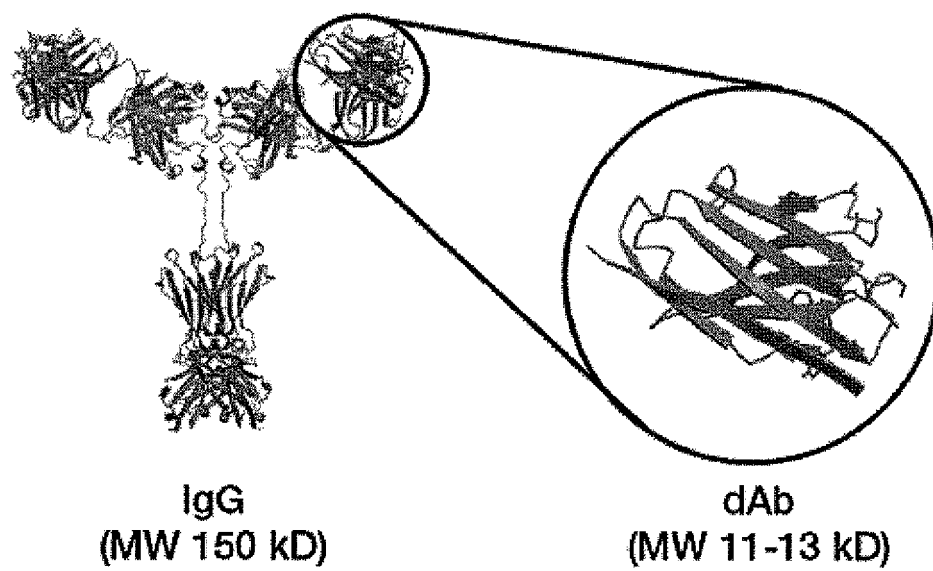
Domain Antibodies

Domain Antibodies (dAbs) are the smallest functional binding units of antibodies, corresponding to the variable regions of either the heavy (V_H) or light (V_L) chains of human antibodies. Domain Antibodies have a molecular weight of approximately 13 kDa, or less than one-tenth the size of a full antibody. Domantis has developed a series of large and highly functional libraries of fully human V_H and V_L dAbs (more than ten billion different sequences in each library), and uses these libraries to select dAbs that are specific to therapeutic targets.

In contrast to conventional antibodies, Domain Antibodies are well expressed in bacterial, yeast, and mammalian cell systems. In addition, many dAbs from Domantis' libraries are highly stable and retain activity even after being subjected to harsh conditions, such as freeze-drying or heat denaturation. These features make Domain Antibodies amenable to a wide range of pharmaceutical formulation conditions and manufacture processes. In addition, the small size of dAbs allows for higher molar quantities per gram of product, which should provide a significant increase in potency per dose and reduction in overall manufacturing cost.

The Domain Antibodies selected against a particular target can be used as a building block to create therapeutic products with unique characteristics not available to conventional antibodies or proteins, such as Dual Targeting dAbs that bind to two therapeutic targets in one easily produced molecule, dAbs with a tailored serum half life, dAbs for pulmonary or oral administration for lung or GI tract diseases, and dAbs against targets that can not be easily addressed by IgGs.





Publications

Jespers, L., Schon, O., Famm, K. & Winter, G (2004). Aggregation-resistant domain antibodies selected on phage by heat denaturation, *Nature Biotechnology*, **22**, 1161- 1165.

Jespers, L, Schon, O, James, L. C., Veprintsev, D & Winter, G. (2004). Crystal Structure of HEL4, a Soluble, Refoldable Human VH Single Domain with a Germ-line Scaffold, *J. Mol Biol*, **337**, 893-903.

Holt, L. J., Herring, C., Jespers, L. S., Woolven, B. P. & Tomlinson, I. M. (2003). Domain antibodies: proteins for therapy, *Trends in Biotechnology*, **21**, 484-489.

De Wildt, R. M., Mundy, C. R. *et al.* (2000). Antibody arrays for high-throughput screening of antibody-antigen interactions, *Nature Biotechnology*, **18**, 989-994.

Tawfik, D. S. & Griffiths, A. D (1998). Man-made cell-like compartments for molecular evolution, *Nature Biotechnology*, **16**, 652-656.

Kristensen, P. & Winter, G. (1998). Proteolytic selection for protein folding using filamentous bacteriophages, *Folding & Design*, **3**, 321-328.

McCafferty, J., Griffiths, A. D. *et al.* (1990). Phage antibodies: filamentous phage displaying antibody variable domains, *Nature*, **348**, 552-554.

Ward, E. S., Gussow, D. *et al.* (1989). Binding activities of a repertoire of single immunoglobulin variable domains secreted from Escherichia coli, *Nature*, **341**, 544-546.

Intellectual Property

Domantis has a broad and dominant patent position in the field of human Domain Antibodies. High affinity single variable domains were first isolated using antibody repertoires at the MRC's Laboratory of Molecular Biology in the late 80's. Domantis has an exclusive licence from the MRC to patent rights covering these inventions, which now consists of multiple issued and pending patents in the US, Europe and other countries. These patent rights cover: Cloning of antibody sequences, expression libraries, and single domain compositions (Winter II); repertoires of antibody molecules, including repertoires of VH and VL sequences (Huse/Lerner/Winter); and phage display of antibody fragments (McCafferty, Griffiths). [See, for example, US Patent 6,291,158; 6,582,915; 6,593,081; 6,172,197; US Serial No. 2004/0110941; European patent application No. 1433846 and European Patents 0368684 & 0616640].

Domantis also owns a number of patent rights that cover dAb libraries, novel selection and screening methods, dAb formats for Dual Targeting, formats conferring extended serum half life, using PEG and AlbudAb™, dAb formulations, and dAb product leads against specific targets and diseases. [See, for example, US Patent 6,696,245, WO05/035572, WO04/101790, WO04/081026, WO04/058821, WO04/003019 and WO03/002609].

The combination of these exclusively licensed and owned patent rights ensures that Domantis will be the only company capable of fully exploiting the commercial applications of human Domain Antibodies.

